

The critical role of cathepsin E/TRAIL system and cathepsin B in the phenotypic change of microglia/macrophages

倪, 軍軍

<https://hdl.handle.net/2324/1654764>

出版情報：九州大学, 2015, 博士（学術）, 課程博士
バージョン：
権利関係：やむを得ない事由により本文ファイル非公開（2）



氏 名 : 倪 軍軍

論 文 名 : The critical role of cathepsin E/TRAIL system and cathepsin B in
the phenotypic change of microglia/macrophages

(ミクログリア/ マクロアージの極性転換におけるカテプシン/ TRAIL システムの役割)

区 分 : 甲

論 文 内 容 の 要 旨

Proteinase cascades are part of the basic machinery of neuronal death pathways. Neuronal cathepsin B (CatB), a typical cysteine lysosomal protease, plays a critical role in neuronal death through lysosomal leakage or excessive autophagy. On the other hand, much attention has been paid to microglial CatB in neuronal death. We herein show the critical role of a proteolytic relay through microglial CatB and cathepsin E (CatE) in polarization of microglia/macrophages to the neurotoxic phenotype, leading to hypoxic/ischemia (HI)-induced hippocampal neuronal damage in neonatal mice. HI caused extensive brain injury in neonatal wild-type mice, but not in CatB^{-/-} mice. Furthermore, HI induced polarization of microglia/macrophages to neurotoxic followed by neuroprotective phenotype in wild-type mice. On the other hand, microglia/macrophages showed only the early and transient polarization to neuroprotective, but not neurotoxic, phenotype in CatB^{-/-} mice. When conditioned medium from cultured microglia polarized to neurotoxic phenotype (M1-CM) was prepared in the presence of a specific CatB inhibitor CA-074Me, the neuronal death of primary cultured hippocampal neurons induced by M1-CM was significantly declined. Furthermore, CA-074Me prevented the activation of nuclear factor- κ B (NF- κ B) in cultured microglia by inhibiting autophagic I κ B α degradation following exposure to oxygen-glucose deprivation, an *in vitro* model of neonatal HI. Rather surprisingly, CatE has been shown to increase the CatB expression after HI by the liberation of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) from microglia through the proteasomal pathway. A significant increase of both CatB and CatE was found exclusively in microglia/macrophages after HI. Thus, a proteolytic relay through the early CatE/TRAIL-dependent and late CatB-dependent pathways may play an essential role in the polarization of microglia/macrophages to neurotoxic phenotype.